EXHIBIT B

WARNING LETTER

Applied Therapeutics, Inc.

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Delivery Method:

VIA UNITED PARCEL SERVICE AND VIA E-MAIL

Reference #:

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Product:

Drugs

Recipient:

Shoshana Shendelman, Ph.D.

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WARNING LETTER 24-HFD-45-11-01

Novermber 27, 2024

Dear Dr. Shendelman:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted between April 29 and May 3, 2024. Investigators Kerun Hardeo, Benton M. Ketron, and Cheryl A. Grandinetti, representing FDA, reviewed the role of Applied Therapeutics, Inc. (Applied Therapeutics) as the sponsor of a clinical investigation (Protocol **(b)(4)**.

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects have been protected.

At the conclusion of the inspection, Investigators Hardeo, Ketron, and Grandinetti discussed with you significant findings and presented the Form FDA 483, Inspectional Observations. We acknowledge receipt of your May 9, 2024, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your written response dated May 9, 2024, it appears that Applied Therapeutics did not adhere to the applicable statutory requirements in the Federal Food, Drug and Cosmetic Act (FD&C Act) and applicable regulations contained in Title 21 of the

Code of Federal Regulations, part 312 (21 CFR 312) governing the conduct of clinical investigations. We wish to emphasize the following:

1. Failure to permit an authorized officer or employee of the Food and Drug Administration to have access to and copy and verify records and reports relating to the conduct of a clinical investigation [21 CFR 312.58].

FDA regulations require sponsors, upon request from an authorized officer or employee of the FDA, at reasonable times, to permit such an officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation. Applied Therapeutics failed to adhere to these requirements.

Specifically, for Protocol **(b)(4)**, Applied Therapeutics used Pearson's Q-global®, a Web-based administration system for capturing data for certain electronic clinical outcome assessments (eCOAs) performed for measuring primary and secondary efficacy endpoints. These eCOAs included the **(b)(4)**.

FDA requested access to verify electronic data collected and maintained in Q-global® during this inspection and during an earlier inspection conducted at one of the **(b)(4)** clinical sites, Site **(b)(4)** between **(b)(4)** and **(b)(4)**.

However, on March 27, 2024, two days after FDA preannounced its inspection of one of the clinical sites, Site **(b)(4)**, a third-party vendor contracted by Applied Therapeutics deleted electronic data in Q-global®, including associated audit trails, for the **(b)(4)** for all 47 subjects enrolled in the study at all **(b)(4)** clinical sites. As a result, during the sponsor inspection, FDA was unable to access and copy and verify records and reports relating to the study conducted under Protocol **(b)(4)** specifically certain electronic data collected and maintained in Q-global® for critical eCOAs for all 47 subjects at multiple study timepoints for this clinical investigation.

We acknowledge that this finding, as included on the Form FDA 483 you received, was limited to the deletion of **(b)(4)** source data for 11 subjects at Site **(b)(4)** and therefore your written response to the Form FDA 483 does not directly address the extent of this finding as discussed in this letter.

In your May 9, 2024, written response, you stated that the deleted **(b)(4)** source data for 11 subjects, which was captured directly into Q-global®, could not be recovered in electronic format. You also indicated that steps have been taken to ensure the integrity of the remaining data. For example, you stated that you instructed **(b)(4)** (the developers of **(b)(4)** to block any further actions regarding data for this study, such that no further data could be deleted. You also stated that **(b)(4)** transferred a copy of the remainder of the electronic dataset to Applied Therapeutics for backups, and the data is now warehoused with both **(b)(4)** and Applied Therapeutics. In addition, you performed an assessment of systems to ensure that the third-party vendor did not have the capability to delete data from any other systems.

You further stated in your May 9, 2024, written response that preventive actions will be taken, including but not limited to the following:

1. For any new trial, Applied Therapeutics will create a data process map that clearly shows the flow and storage of collected data, to ensure that source data is maintained at both the site and at the sponsor.

2. Original paper source documents will remain at the clinical site, with a PDF copy available at the sponsor.

3. Electronic data (even if held on third-party systems) will be backed up appropriately and held at the sponsor.

4. External vendors will not have the ability to delete files from any electronic systems.

5. Appropriate electronic audit trails will be maintained such that any changes to electronic data will be identifiable and auditable.

FDA acknowledges that, in an August 27, 2024, written response to FDA's August 20, 2024, Information Request, Applied Therapeutics stated that an export of the **(b)(4)** data from the backup Q-global® system is maintained with a third-party statistical consulting vendor; however, the data is no longer available in Q-global®.

FDA also acknowledges that, in a September 11, 2024, written response to FDA's September 5, 2024, correspondence providing the Late Cycle Meeting Background Package, Applied Therapeutics stated that the third-party vendor deleted the data **(b)(4)** from the Q-global® system without consulting Applied Therapeutics, the sponsor. Applied Therapeutics also stated that it was able to recover this data from the Q-global® system's backup, except for the 11 **(b)(4)** tests. Applied Therapeutics noted that, before the electronic data's deletion, item-level responses were captured in PDF and in paper copies of the score reports.

While we acknowledge Applied Therapeutics' response, as well as the corrective and preventive actions that Applied Therapeutics has taken and plans to take, your response is inadequate because you did not include sufficient details about your corrective action plan. For example, you did not provide sufficient details regarding the procedures being implemented to prevent similar violations in the future. Additionally, we remain concerned that electronic data collected for critical eCOAs was deleted and cannot be verified, which raises concerns about the validity and integrity of the data collected during the clinical investigation. Without access to the pertinent electronic data in Q-global®, including associated audit trails, FDA cannot verify the accuracy, consistency, and completeness of study data collected for critical eCOAs used to measure primary and secondary efficacy endpoints, and cannot evaluate the extent and impact of any reported data errors and discrepancies. FDA also cannot confirm whether the clinical investigation was conducted in compliance with the regulatory responsibilities set forth in 21 CFR 312.

2. Failure to provide FDA [with] a description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers [21 CFR 314.50(d)(5)(iv)].

In order to permit FDA to make a knowledgeable judgment about a new drug application, FDA regulations require applicants for new drug applications to provide FDA with a description and analysis of any data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, including information derived from clinical investigations. Applied Therapeutics, as the applicant of **(b)(4)** failed to adhere to this requirement.

Specifically, according to Applied Therapeutics' October 19, 2023, Clinical Study Report for Protocol **(b)(4)** which was submitted to FDA on December 28, 2023, the **(b)(4)** was provided by **(b)(4)** as a **(b)(4)** mg/mL **(b)(4)**.

However, during FDA's inspection of Site **(b)(4)** FDA found that **(b)(4)** had supplied the clinical sites for Protocol **(b)(4)** with **(b)(4)** mislabeled as **(b)(4)** mg/mL, when in fact the amount of **(b)(4)** supplied by **(b)(4)** was **(b)(4)** mg/mL. As a result of this error, between March and June 2021, clinical sites administered 80% of the protocol-required dose to subjects.

Specifically, at least 19 subjects at Site **(b)(4)** received a lower dosage of the **(b)(4)** than the protocol required. On June 17, 2021, Applied Therapeutics notified clinical sites of this error, and on June 29, 2021, clinical sites were provided with a new formulation of the **(b)(4)** at the correct concentration of **(b)(4)** mg/mL. Clinical sites were also provided with an updated version of the pharmacy manual, with instructions on drug administration.

Applied Therapeutics failed to provide FDA with any description or analysis of the information describing the nature and extent of the dosing errors related to the mislabeled **(b)(4)**. Specifically, Applied Therapeutics reported dose levels for subjects as stated in the protocol (for example, **(b)(4)** mg/kg), rather than the actual dose levels administered. Information on the nature and extent of the dosing errors is relevant to an evaluation of the safety and effectiveness of the investigational drug product. Therefore, Applied Therapeutics failed to provide sufficient information at the time of submission of the application to enable FDA to make an informed decision regarding the impact of the dosing-error incident on study data. This failure raises significant concerns about the validity, reliability, and integrity of the data for Protocol **(b)(4)**. Furthermore, Applied Therapeutics' failure to disclose this critical information raises significant concerns about the sponsor's oversight and conduct of clinical investigations, including its compliance with the reporting requirements for human drug products.

We acknowledge that this finding was not included on the Form FDA 483 you received, and therefore your written response does not address this finding.

We emphasize that as a sponsor, Applied Therapeutics has ultimate oversight of the clinical investigation, and was responsible for ensuring compliance with all applicable FDA regulations governing the conduct of clinical investigations. Applied Therapeutics' failure to permit FDA access to verify records and reports related to a clinical investigation, and its failure to provide FDA information relevant to an evaluation of the safety and effectiveness of an **(b)(4)** raise significant concerns about the validity and reliability of data collected for this clinical investigation.

This letter is not intended to be an all inclusive list of deficiencies with your clinical study of an **(b)(4)**. As the sponsor, it is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address any deficiencies and establish procedures to ensure that any ongoing or future studies comply with FDA regulations.

This letter notifies you of our findings and provides you with an opportunity to address the above deficiencies. Within 15 business days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to address this matter adequately may lead to regulatory action. If you believe that you have complied with the FD&C Act and relevant regulations, please include your reasoning and any supporting information for our consideration.

Should you have any questions or concerns regarding this letter or the inspection, please email FDA at CDER-OSI-Communications@fda.hhs.gov. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,

{See appended electronic signature page}

David C. Burrow, Pharm.D., J.D.

Director

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/s/

DAVID C BURROW

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